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Abstracts

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Antithrombotic activity of the glomerular basement membrane (GBM) of the rat kidney is dependent on glomerular ADP-ase activity. *W.W. Bakker, E.J. Willink, M.J. Hardonk, Department of Pathology, University of Groningen, Groningen, The Netherlands.* Recently the activity of nucleoside polyphosphatases, including ADP-ase, has been demonstrated in situ throughout the GBM of the normal rat kidney using cytochemical methods at the ultrastructural level. To investigate the possible influence of glomerular ADP-ase activity upon experimentally–induced intraglomerular platelet aggregation, we carried out alternate perfusion experiments with human platelets and ADP in rat kidneys ex vivo, taking advantage of previous results showing that either injection of adriamycin (ADR) (7.5 mg/kg body wt) or local X-irradiation (Xirr, 2000 rads) reduces glomerular phosphatase activity, whereas injection of an other nephrotoxic drug, that is, aminonucleoside of puromycin (PAN) (15 mg/kg body wt) does not affect this enzyme activity. Kidneys of inbred PVG rats 24 hr after treatment with either ADR ($N = 5$); PAN ($N = 4$), or Xirr ($n = 3$) or untreated rats ($N = 6$), were perfused ex vivo with buffered saline (PBS) 37°C, pH 7.2, to remove blood and subsequently with 4 ml PBS containing 1 μg/ml endotoxin to facilitate intraglomerular platelet accumulation. Subsequently, alternate perfusion (flow rate 2 ml/min) with 4 ml human platelet–rich plasma (PRP) (9×10^5 platelets/ml) was followed by 4 ml ADP (10 μg/ml) in PBS, and again 4 ml PRP was carried out. Kidneys were taken out and processed for light (LM), immunofluorescence (IF) and electron microscopy (EM). The results show intraglomerular platelet aggregation in about 50% of the glomeruli of both ADR as well as Xirr rats, in contrast to PAN-treated or normal rats in which no platelet aggregation could be detected using LM. Using EM and IF accumulation of activated platelets and deposition of products from activated platelet, that is, platelet factor 4 and β-thromboglobulin, could be detected along the GBM exclusively in kidneys of ADR treated or Xirr rats. Since glomerular ADP-ase activity, in contrast to other putative antithrombotic molecules in the GBM, that is, heparan sulphate proteoglycans, is clearly affected by ADR treatment or X-irradiaton, it is concluded that the activity of glomerular ADP-ase may reflect an important antithrombotic principle in the GBM of the rat kidney.

The role of complement in the heterologous phase of anti-GBM nephritis in the mouse. *G. Schrijver, K.J.M. Assmann, M.J.J.T. Bogman, R.A.P. Koene Dep. of Pathology and Dep. of Medicine, Div. of Nephrology, St. Radboud Hospital, University of Nijmegen, Nijmegen, The Netherlands.* Anti-GBM nephritis was induced in B10.D2 mice by injection of heterologous antibodies against mouse GBM. Histologically, the glomeruli showed linear deposits of the injected antibody along the GBM together with granular deposition of C3, intravascular influx of polymorphonuclear granulocytes (PMNs), and deposition of fibrin. This heterologous phase was accompanied by a dose dependent albuminuria. When a low dose of antibody was injected into congenic mice with a complete congenital deficiency of complement factor C5 (B10.D2/old) the albuminuria was greatly reduced. However, when the antibody dose was raised, the reduction in albuminuria was less pronounced.

Antibody Dose (mg)	Albuminuria ± SD at day 1 (μg/18 hr)		
	B10.D2/new	B10.D2/old	*P*
1.9	1252 ± 466	531 ± 196	<0.0007
7.5	8895 ± 4011	4127 ± 1909	NS

Comparable results were found in B10.D2/new mice made completely deficient of C3 by Cobra Venom Factor (CVF) treatment. Despite the complete absence of C3 deposits in the glomeruli of the CVF-treated mice, the PMN influx in the glomeruli was similar to that seen in complement–normal B10.D2/new mice, reaching a maximum at two hours after injection of the antibody. Deposition of fibrin was first present at two hours and increased thereafter both in complement–normal and complement–deficient mice. We conclude that in this model there are at least two pathways leading to albuminuria, one of which is complement–dependent. The mediator system of the complement–independent pathway is unclear. PMNs invading the glomeruli despite the complement depletion may release mediators that increase the permeability of the capillary wall. Intravascular coagulation may also play a role.

Follow-up of renal function and proteinuria in rats with a reduced number of nephrons on various protein diets. *M.H. De Keijzer, A.P. Provoost, E.D. Wolff, and J.C. Molenaar. Depts. of Pediatric Surgery and Pediatrics, Erasmus University, Rotterdam, The Netherlands.* A reduction in the number of functioning nephrons may in the long run lead to the development of end stage renal failure. This process may be attenuated by a reduction in the daily protein intake. In rats, we wanted to establish the degree of reduction in function initiating this process and study the long–term effects of various protein intakes on the glomerular filtration rate (GFR) and the urinary protein excretion ($U_{prot}V$). Nine experimental groups, initially consisting of 17 to 24 rats were studied. In three–weeks–old male Wistar rats we applied three types of operations: sham operation (2K), unilaterally nephrectomy (NX), and a temporary ureteral obstruction plus removal of the contralateral intact kidney (UO). Three diets were used, containing either 12%, 24%, or 36% of protein. The GFR, as the plasma clearance of 51-Cr EDTA, and the $U_{prot}V$ were determined every three months. The follow up time is now 18 months, that is, about half of the expected lifetime. The data on the GFR (ml/min) and $U_{prot}V$ (mg/24h) are given at 3, 12, and 18 months. The data are expressed as a % of the 2K rats on the 24% protein diet at three months.

GFR ml · min^{-1}

	3 months			12 months			18 months			
RAT:	12%	24%	36%	12%	24%	36%	12%	24%	36%	diet
2K:	92	100	108	97	105	128	100	108	117	
NX:	63	77	82	70	81	69	71	55	32	
UO:	56	59	60	35	22	6	14	NS	NS	

$U_{prot}V$ mg · 24 hr^{-1}

2K:	108	100	151	58	89	257	49	132	257	
NX:	103	149	268	249	552	942	277	837	933	
UO:	248	370	573	997	1342	1723	1075	NS	NS	

NS = no surviving animals

The results indicate that in 2K rats, up to 18 months, the daily protein intake did not adversely affect the GFR. On a high protein diet 2K rats showed an increase in $U_{prot}V$. In NX rats, the GFR deteriorated with time on both the 24% and 36% protein diet. The fall in GFR occurred earlier on the 36% protein diet, and was preceded by a rise in $U_{prot}V$. The NX rats on a low protein diet showed no fall in GFR, but $U_{prot}V$ was increased compared that of 2K rats on the same diet. The most dramatic effects were noted in the UO rats. At three months, the GFR was over 75% of that of NX rats on the same diet. The $U_{prot}V$ was already markedly increased. On all three diets GFR fell rapidly, the highest rate on the 36% and the lowest rate on the 12% protein diet. At 18 months there were no survivors in the groups of UO rats on a normal and high protein diet. We conclude that in rats with a slightly damaged single kidney a low protein diets delays, but not prevents, the development of end stage renal failure.

The technique of the isolated perfused rabbit tubule (IPRT) and its use in exploring pharmacokinetics of indomethacin. *D. de Zeeuw, H.R. Jacobson, and D.C. Brater, University Hospital, Groningen, The Netherlands, and UTHSC at Dallas, USA.* Renal secretion of drugs via the tubular organic anion transporter has been studied by various in vitro and in vivo techniques. All have their limitations. The IPRT has the qualities and thereby offers opportunities that allow further characterization of the organic anion transport system(s). The relevant tubule segment, that is, the proximal straight tubule is dissected free hand from a rabbit kidney slice. The tubule is transferred to a microperfusion set-up consisting of a transmission microscope fitted with steady supports at both sides. These enable micromanipulation of concentric glass pipets that will hold the tubule. The tubule is bathed in a flowing bath solution at 38°C. The proximal end of the tubule is canulated with a glass pipet and perfused with an ultrafiltrate-like solution. The distal end is sucked into a holding pipet allowing perfused fluid collection. Samples are taken using a constant-volume pipet. Tubular quality and viability control is carried out by measurement of the transepithelial voltage, and by a measurement of water reabsorption along the tubule (J_v) using ^{3}H-inulin as a marker. We developed a highly sensitive HPLC-assay for indomethacin measurement (as low as 10 pg). This allowed measurement of native (non-labeled) drug in the very small collected samples (100 nl). Thus indomethacin transport from bath to lumen (J_{ind}) could be estimated using close to pharmacological indomethacin bath concentrations (10^{-6}M). A series of 33 experiments with varying concentrations of indomethacin in the bath fluid disclosed that J_{ind} obeys laws of saturable kinetics ($V_{max} = 115 \times 10^{-15}$M/mm/min, $K_m - 6 \times 10^{-6}$M). Cooling of the tubule to 18°C reduced J_v from 0.39 ± 0.06 to −0.02 ± 0.01 nl/mm/min, whereas J_{ind} was inhibited only by 52 ± 5% ($N = 12$). Moreover, ouabain and the use of sodium-free solutions also reduced J_{ind} to half of control values ($N = 6$). This strongly suggests that J_{ind} is partly mediated by a secondary active sodium coupled transporter. Probenecid and PAH at different concentrations showed a competitive inhibition of J_{ind} ($N = 10$). Both compounds were able to completely abolish J_{ind} (10^{-6}M bath) at bath concentrations of 2×10^{-5}M probenecid and 2×10^{-3}M PAH. Furthermore, the disulfonate stilbene DIDS (an anion exchange inhibitor) inhibited J_{ind} of the cooled tubule to zero ($N = 8$). In conclusion, the IPRT is a technique suited for studying renal secretion of drugs. Indomethacin is excreted into the lumen of the rabbit proximal straight tubule. The affinity of indomethacin for the carrier is higher than that of probenecid and PAH. At least half of the transport is active. The remaining passive component is inhibited by probenecid and DIDS, suggesting the presence of an anion exchanger for indomethacin transport.

Sensitivity of screening methods for renovascular hypertension can be improved: First experiences with a new animal model. *G.J. Jonker, D. de Zeeuw, R.M. Huisman, G.K. van der Hem, Department of Nephrology, State University Groningen, Groningen, The Netherlands.* Diagnosis of renovascular hypertension is frequently hampered by false-negative rapid-sequence IVU (rs-IVU) or renography (RE). Probably in these cases the presence of renal artery stenosis is obscured by renal autoregulation. The latter is critically dependent upon the renin-angiotensin and the prostaglandin systems. We developed an animal model to answer the question whether drugs blocking these systems will decrease autoregulatory capacity to such an extent that the sensitivity of rs-IVU and RE as screening methods is enhanced. As a model, the salt-depleted chronically-instrumented conscious dog was chosen. The instrumentation consists of permanent arterial and venous catheterization, electromagnetic flow probes around both renal arteries and a newly developed constrictor device around one of the renal arteries. This constrictor is externally adjustable via a hydraulic mechanism and the applied constriction remains stable through a mechanical catch. Furthermore, a new method was evaluated to obtain a reference zero (no blood flow) value for the electromagnetic blood flow measurement. Pharmacologically obtained diastolic zero flow by intra-aortic injection of angiotensin II compared favorably with a mechanical occlusion, and it appeared to be an easily reproducible method. In this model, data before and after renal artery constriction were compared. After a recovery period of two to three weeks, control rs-IVU and ^{123}I-hippuran RE were performed before and after intravenous administration of 10 mg enalaprilic acid (MK-422). Blood pressure and renal blood flow were registered before and during both procedures. Various degrees of stenosis were made, and two to three weeks later the "diagnostic" measurements were repeated. Four dogs have presently finished this protocol. In the control period no differences between the two kidneys were observed. The outcome of these measurements did not change after MK-422 injection. Interestingly, following mild to moderate stenosis (that is, 25 to 60% flow reduction), rs-IVU as well as RE showed no or only slight differences between the post-stenotic and the contralateral kidney. However, after MK-422 there were marked differences between the two kidneys. Thus, preliminary results of this new model to study renal artery stenosis in the conscious dog indicate that the sensitivity of both rs-IVU and RE can be improved by acute converting enzyme inhibition.

Inhibition of drug protein binding (PB) in uremia. *R. Vanholder, N. Van Landschoot, R. De Smet, S. Ringoir, Renal Division, University Hospital, 9000 Ghent, Belgium.* The influence of renal failure on protein binding (PB) of several drugs was evaluated by an ultrafiltration method. The study was performed in normal serum, serum of patients with moderate and pronounced chronic renal failure (serum creatinine < 1.3, 3 to 6 and > 6 mg/dl, respectively) and serum of patients under hemodialysis treatment. No significant changes were registered for cimetidine and imipramine. A progressive decrease in PB related to the degree of renal failure was observed for diazepam, theophylline, methotrexate, phenytoine, and prazosine. The alterations were most pronounced for theophylline (from 64.7 ± 0.5 in healthy controls to 43.5 ± 4.1 % in dialyzed patients), methotrexate (from 47.9 ± 3.3 to 27.4 ± 2.3 %) and phenytoine (from 91.6 ± 0.2 to 75.6 ± 2.9 %) ($P < 0.001$). Hemodialysis caused no major changes in PB of all drugs under study. Ultrafiltrate, obtained during a hemofiltration session, inhibited PB of theophylline and phenytoin in a dose-dependent way. After separation with high performance liquid chromatography (HPLC), it appeared that at least a part of this inhibitory activity corresponded to the elution zone of hippurate. Also this inhibition was dose-dependent. Hippuric acid solution inhibited PB of theophylline and phenytoine in direct relationship to its concentration. In conclusion, PB of several drugs is affected during renal failure, which might influence their therapeutic effectiveness. Hippuric acid is one of the uremic solutes playing a role in this process.

EDTA Lead-mobilization test and bone lead concentration in occult lead intoxication. *R. Daelemans, G. Eestermans, P. D'Haese, F.L. Van de Vyver, P. Zachée, R.L. Lins, G.A. Verpooten, R.P. Weeden, M.E. De Broe, A.Z. Stuivenberg, University Hospital Antwerp, Antwerpen, Belgium.* In 35 patients (pat.), suspected of occult lead (Pb) intoxication, an EDTA Pb-mobilization test was performed by intramuscular injections of 2 × 1 g $CaNa_2$ EDTA, 8 hours (hr) apart. Urinary Pb excretion (UPb) was measured by electrothermal atomic absorption spectrometry (EAAS) in 24 hr urine samples in pat. with a serum creatinine (sc) < 1.5 mg/dl and extended to 72 hr when sc > 1.5 mg/dl. The test was considered positive if UPb > 1000 μg, negative if UPb < 600 μg and inconclusive when 600 μg < UPb < 1000 μg. 16 pat. (46%) had a mean UPb of 1852 μg (1095–3700) (group I), 14 pat. (40%) a mean UPb of 344 μg (160–517) (group II), and 5 pat. (14%) a mean UPb of 753 μg (671–870) (group III). There was no significant difference in renal function in the 3 groups. Blood lead concentration (BPb), free erythrocyte protoporphyrin (FEP) and urinary delta-ALA were below internationally accepted standards in all pat. Transiliac bone biopsies were

performed in 7 pat. of group I and 6 pat. of group II. Bone lead concentration (BLC) determined by EAAS after destruction with nitric acid, was respectively 26 ppm (14.5–33) in group I and 4 ppm (2.1–6.7) in group II. There is a significant correlation (r = 0.94) between BLC and UPb. BLC = 1.24 + 0.01267 UPb. *Conclusion*:

1. 46% of pat. suspected of occult Pb intoxication had a positive EDTA test.
2. BPb, FEP and delta-ALA are of no value in this setting.
3. A positive EDTA test is indicative of excessive body Pb burden as measured by transiliac BLC.

Causes and prognosis of acute renal failure (ARF) in the elderly. *N. Lameire, E. Matthys, R. Vanholder, S. Ringoir, Gent, Belgium.* The question of old age as a negative prognostic factor in the outcome of ARF is still controversial. Therefore, a retrospective analysis of the causes and diagnostic and prognostic parameters of ARF was made over the years 1980–1985 in one single renal unit, where all cases were treated in a similar aggressive way. One hundred patients older than 65 years (Group I) were compared with 187 younger patients (Group II). There was a higher incidence of postrenal ARF (9 vs. 4.8%), thromboembolic diseases (8 vs. 1.6%) and hypovolemic ATN (19 vs. 9%) in Group I, while non-oliguric ARF (19 vs. 38%), acute glomerulonephritis (5 vs. 11.%) and pigment–induced ARF (4 vs. 12.8%) were less frequent in this group. An analysis of the diagnostic value of the urinary parameters (RFI & FE_{Na}) revealed that in Group I 21% and in Group II 15% of the values indicated prerenal ARF; this diagnosis could not be accepted on clinical and/or histological grounds. Prognosis in both groups was mainly related to the number of complications arising during hospitalization. In Group I, the presence of initial hypokalemia and metabolic alkalosis was associated with a very high mortality (>70%). The overall mortality, however, was the same in both groups (46% in Group I vs. 44% in Group II). There was no correlation between mortality and the applied dialysis strategy (acute peritoneal dialysis or hemodialysis). In conclusion, the prognosis of ARF is independent of age, and elderly patients with ARF should be treated in the same aggressive way as younger patients.

Adrenergic vasoconstriction in the human hypertensive kidney: Overriding role of alpha-2 adrenoceptors. *P.W. de Leeuw, P.N. van Es, P. Vermey, W.H. Birkenhäger. Department of Medicine, Zuiderziekenhuis, Rotterdam, and Department of Pharmacy, University Hospital, Leiden, The Netherlands.* Adrenergic vasoconstriction contributes to the elevation of renal vascular resistance in essential hypertension, but it is not well known which type of alpha–adrenoceptors is involved in this process. Therefore, we infused either the alpha-1 antagonist doxazosin ($N = 7$) or the alpha = 2 antagonist yohimbine ($N = 7$) into the renal artery of hypertensive subjects immediately prior to diagnostic angiography. Doxazosin was administered at incremental doses of 0.3, 1, and 3 ng kg^{-1} min^{-1} and yohimbine at doses of 1, 3, and 10 ng kg^{-1} min^{-1}. Each dose was given for five minutes; a group of six patients in whom only vehicle was infused, served as a control group. Before the infusions and at the end of each dose intra-arterial blood pressure and mean renal blood flow (Xenon–washout) were measured. Doxazosin increased renal perfusion without changes in blood pressure at doses of 0.3 and 1 ng kg^{-1} min^{-1}, with the highest dose systemic effects occurred leading to a fall in blood pressure. Yohimbine also increased renal flow without changes in pressure at doses of 1 and 3 ng kg^{-1} min^{-1}, but reduced perfusion and increased blood pressure at the highest dose. At the intermediate doses, doxazosin increased renal blood flow from 342 ± 36 to 380 ± 45 ml min^{-1} per 100 g ($P < 0.05$) while yohimbine enhanced flow from 318 ± 41 to 500 ± 62 ml min^{-1} per 100 g ($P < 0.01$). The increment in flow produced by yohimbine greatly exceeded that caused by doxazosin ($P < 0.05$). It is concluded that for a given level of blood pressure prevailing sympathetic activity elevates vascular tone in the kidney predominantly through alpha-2 adrenoceptors.

Mononuclear blood cells from patients with minimal change nephrotic syndrome (MCNS) induce increased glomerular permeability in the rat kidney in vivo. *W.W. Bakker, J. Baller, W.H.J. van Luyk, G.K. van der Hem, Departments of Pathology, Pediatrics and Internal Medicine, University Hospital Groningen, Groningen, The Netherlands.* Peripheral mononuclear blood cells (PBC) from nephrotic and control subjects were isolated to investigate their capacity to induce increased glomerular permeability in vivo in the rat kidney. Blood was taken from untreated subjects with MCNS in relapse (selective proteinuria > 3 · 5 g/24 hr; $N = 4$) and in remission under corticosteroid treatment. In addition, untreated subjects with non-selective proteinuria due to other forms of nephropathy ($N = 5$) and healthy donors ($N = 5$) were studied. Individual cell suspensions (20×10^6/3 ml per 150 g body wt) in buffered saline were infused in the cannulated tail vein of anesthesized inbred PVG rats using a constant infusion pump at a flow rate of 0.2 ml/min followed by 2 ml anionic ferritin (76 mg/150 g body wt). After an additional period of 15 minutes, the animals were sacrificed and their kidneys prepared for transmission electron microscopy (EM). The localization of ferritin particles in the glomerular filtration barrier was evaluated semiquantitatively in capillary loops of six glomeruli per kidney. The results can be summarized as follows: exclusively in rats, which had been infused with cells from MCNS subjects in relapse, ferritin particles could be detected in the lamina rara interna (LRI), lamina densa (LD), lamina rara externa (LRE), and between foot processes at several sites along the capillary loops studied. In contrast, neither following infusion of PBC from the same MCNS subjects in remission nor from other subjects studied penetration of ferritin particles into the LD, LRE or urinary space could be observed. Localization of ferritin was confined in these cases to the LRI of the filtration barrier. It is suggested from the present data that PBC from nephrotic patients with MCNS are able to change glomerular permeability in the rat kidney in vivo. In view of the current idea of a circulating "factor" in the pathogenesis of proteinuria in this disorder, the possibility emerges that a circulating PBC subset may be a likely candidate for such a putative factor in MCNS.

Tubular sodium (Na)-handling during mineralocorticoid escape (ME): An analysis using free water and lithium clearance. *W.H. Boer, H.A. Koomans, E.J. Dorhout Mees, Department of Nephrology, University Hospital, Utrecht, The Netherlands.* The established technique to study tubular Na handling inman is the maximal free water clearance. Using this technique, ME has previously been shown to result from a rise GFR and a decrease in fractional proximal reabsorption (FPR). The model of ME was chosen to test lithium (Li) as a quantitative marker of proximal Na reabsorption. Simultaneous free water ($C\text{-}H_2O$) and Li clearances (C-Li) were performed in eight normal men prior to and after six days of fludrocortisone acetate, when all had escaped from its Na retaining effect. FPR was calculated from $C\text{-}H_2O$ as well as C-Li ($FPR\text{-}H_2O$ and FPR-Li, respectively). All changes were significant ($P < 0.001$).

GFR	$C\text{-}H_20$	C-Li	$FPR\text{-}H_2O$	FPR-Li
Control 125 ml/m	15 ml/m	42 ml/m	85.7%	67.5%
Escape 149 ml/m	24 ml/m	76 ml/m	81.3%	49.7%

As shown, the Li-method yields much lower control values for FPR than the conventional method. It confirms that FPR is depressed during ME, but the observed fall (18%) is much more pronounced than obtained by the $C\text{-}H_2O$ method (4%). Consequently, distal Na delivery increases from 5.8 to 11.1 mmol/min as compared to a change from 2.5 to 3.9 mmol/min calculated from $C\text{-}H_2O$. We suggest that the values obtained by the Li-method are closer to reality, the differences between both methods being mainly due to H_2O backdiffusion, even during maximal ADH suppression.

Aluminum levels, desferrioxamine tests and aluminum bone deposits in a chronic hemodialysis population. *R.M. Valentijn, J.W. de Fyter, V.E.F. Papapoulos, Department of Nephrology and Pathology, University Hospital, Leiden.* In a chronic hemodialysis population the incidence of elevated aluminum levels, the response to desferrioxamine (DFO) stimulation and the occurrence of bone aluminum deposits were studied. In addition, the results were related to hormonal or histological parathyroid activity. In 40 patients, 425 aluminum levels were determined at regular intervals during a two year follow-up. In 14 patients, aluminum levels were < 80 μg/liter at all times, and in 16 patients increased levels were found during 48 episodes. During eight episodes

(six patients) the aluminum levels were > 200 μg/liter. No relation with MCV, Ca, PO_4, alkaline fosfatase or ferritine could be found. DFO-stimulation tests (20 mg DFO/kg body wt i.v.) were performed in 30 patients. An abnormal response to DFO was noted in ten cases. In eight of these cases the baseline aluminum levels before DFO-testing was < 100 μg/liter. Aluminum bone deposits were found in 11 of 18 bone biopsies, and in six of the 11 cases an abnormal DFO-test was found, while the DFO-test was also abnormal in three of the seven cases without bone aluminum deposits. The relationships with parathyroid status showed the following: six of the eight episodes with baseline aluminum levels > 200 μg/liter occurred in patients with a recent (mean 15.5 months) parathyreoidectomy (PTX); an abnormal DFO-test was mainly found in patients with active hyperparathyreoidism based on i-PTH levels ($N = 6$) or bone histology ($N = 5$); six of the seven patients with a recent PTX had positive aluminum bone deposits; the Δ aluminum after DFO was correlated with the PTH level. In patients with PTH levels ≦ 3 the Δ aluminum was 146 ± 87 μg/liter, while in patients with PTH levels > 13 the aluminum was 296 ± 150 μg/liter while in both groups aluminum bone deposits were present. In conclusion we found that: baseline aluminum levels are frequently elevated in a chronic hemodialysis population; DFO-stimulation tests provide useful information, also in cases with low baseline aluminum levels; the response to DFO-stimulation is correlated with parathyreoid activity, and after successful PTX a high incidence of aluminum bone deposits is found.

Late conversion from cyclosporin to azathioprine one year after cadaveric renal transplantation. *D.J. Versluis, F.H.M. Derkx, G.J. Wenting, M.A.D.H. Schalekamp, W. Weimar, Department of Internal Medicine I, University Hospital Rotterdam–Dijkzigt, Rotterdam, The Netherlands.* The results of organ transplantation have significantly improved after the introduction of cyclosporin A (CsA). Unfortunately CsA is nephrotoxic and could lead to irreversible and progressive nephropathy. To avoid these long term sequelae conversion from CsA to azathioprine (AZA) has been suggested. Several studies indeed showed an improvement of renal function after stopping CsA at three or six months after transplantation. However, these early conversions resulted in a high incidence of allograft rejection. In an attempt to induce a safer engraftment, we continued CsA therapy for one year in 23 cadaveric renal allograft recipients before switching to AZA. CsA was stopped and AZA (2 mg/kg) was introduced the next day. All other medication, including 10 to 15 mg prednisone was continued. Within three months after conversion five of 23 patients showed acute rejection; four of five were recipients of second grafts ($P < 0.01$); two of five lost their graft. One of 23 had recurrence of primary disease. In the remaining 17 successfully converted patients we studied the reversibility of CsA toxicity. Three months after conversion ERPF (^{131}I Hippurate) had increased from 216 to 250 ml/min and GFR (^{125}I Thalamate) from 65 to 72 ml/min. Serum creatinine dropped from 160 to 128 μmol/l, while creatinine clearance improved from 46 to 59 ml/min. Blood pressure (Datascope^{R}) decreased in all 17 patients: 140/91 to 119/77; renin levels increased from 10.7 to 16.7 μU/ml. All these changes were highly significant ($P < 0.01$). We also observed that serum cholesterol significantly fell from 7.8 to 6.2 mmol/liter with a concomitant decrease in triglycerides from 2.80 to 2.18 mmol/liter. The two hours glucose levels after oral GTT also significantly dropped from 6.7 to 5.0 mmol/liter. The reversibility of nephrotoxic and metabolic side effects of CsA after one year of continuous therapy suggests that no permanent structural damage had developed, which refutes a main argument for conversion. Moreover, the risk of rejection following conversion still remains high even after one year of CsA therapy especially in recipients of second allografts.

Renal tubular function in amyloidosis. *S. Janssen, S. Meijer, D.A. Piers, M.H. van Rijswijk, G.K. van der Hem, Department of Medicine, University Hospital, Groningen, The Netherlands.* Renal involvement is a major cause of morbidity in patients with amyloidosis. Histological studies indicate that renal failure might develop not mainly as the result of glomerular, but as the consequence of vascular amyloid deposition, resulting in interstitial fibrosis wih concomitant tubular atrophy. This would imply that tubular function is impaired in renal amyloidosis and that measurement of the degree of tubular dysfunction might provide information on the degree of interstitial fibrosis. To test this hypothesis we studied tubular function on 35 occasions in 22 patients with biopsy–proven renal amyloidosis. Proximal tubular function was measured by the relative clearance of ^{99m}Tc-dimercaptosuccinate (RelCl^{99m}Tc-DMSA) using a continuous infusing technique with simultaneous determination of the glomerular filtration rate (GFR) using the clearance of ^{125}I-iothalamate; the relative clearance of ^{99m}Tc-DMSA is expressed as the ^{99m}Tc-DMSA to the ^{125}I-iothalamate clearance × 100% (normal value ≦ 16%). The degree of interstitial fibrosis in renal biopsies was estimated semiquantitatively. Fifteen patients with nonamyloidotic glomerular diseases served as controls. There was no difference in GFR between the controls and the amyloid patients. The RelCl^{99m}Tc-DMSA was less than 16% in the controls irrespective of the degree of renal function loss measured by the GFR, whereas in amyloid nephropathy the RelCl^{99m}Tc-DMSA was elevated in 86%. Our results indicate that proximal tubular dysfunction is a frequent finding in renal amyloidosis and that an increased filtered load (GFR × serum ^{99m}Tc-DMSA activity) does not contribute to an increased urinary excretion of ^{99m}Tc-DMSA. In the amyloid patients there appeared to be a negative correlation between GFR and RelCl^{99m}Tc-DMSA ($r = 0.6826$, $P < 0.001$). Furthermore, the degree of interstitial fibrosis as observed in the renal biopsies showed a distinct positive correlation with tubular dysfunction measured by the RelCl^{99m}Tc-DMSA. These findings confirm the value of the RelCl^{99m}Tc-DMSA as a non-invasive test for the degree of interstitial fibrosis in amyloid nephropathy and contribute to a better understanding of the mechanism of renal function loss in renal amyloidosis.

Renal and systemic effects of atrial natriuretic peptide (ANP) in essential hypertension (EH): Preliminary results. *W.M.T. Janssen, P.E. de Jong, G.K. van der Hem, D. de Zeeuw. Division of Nephrology, State University Hospital, Groningen, The Netherlands.* Synthetic human ANP was infused during four hours at doses of 0.5 and 1.0 μg/min in three patients with EH when they adhered to a diet with 200 mmol NaCl, and at doses of 0.125, 0.25 and 0.5 μg/min in balance on a 50 mmol NaCl diet. No effect on systemic blood pressure (BP) or even a pressor response was observed on doses of 0.125 at low, and 0.5 at the high sodium intake. The higher doses caused a distinct drop in BP. Thus, a steep dose–response relation was observed. Interestingly, a higher BP-response was seen during low salt intake. BP decreased mainly during the last two hours of infusion, sometimes with severe hypotensive complaints. We, therefore, were limted to evaluation of the renal effects in the first two hours of infusion. We focused on the question whether renal hemodynamic, diuretic, and natriuretic responses coincided with BP responses. ERPF showed a marked decrease of about 10%, independent of sodium balance as well as of the ANP dose. Changes in GFR were small, except for the 1 μg/min dose where a 10% increase was observed. At the 50 mmol NaCl intake, no change in urine flow occurred at the 0.125 and 0.25 μg/min doses, whereas a twofold increase was seen at the 0.5 dose. At the high sodium diet, urine volume increased about two times at both doses. Sodium excretion showed a similar pattern as urine volume. Urinary sodium increased 50% at the two lowest doses of ANP during the low sodium diet. During all other infusions sodium excretion about doubled. We conclude that ANP shows a steep dose–response effect on BP during both high and low salt intake, with a higher sensitivity on the low diet. Furthermore, ANP decreases ERPF independent of sodium status as well as of the ANP dose. Diuretic and natriuretic responses are only dose related at the low sodium status. We suggest that renal responses to exogenous ANP precede the BP response. A non-hypotensive dose already elicits diuretic and natriuretic properties.

The influence of a high protein (HP) versus a low protein (LP) diet on the kidney function in moderate to severe renal insufficiency. *G.H. Schaap, H.J.G. Bilo, T.H.R. Alferink, P.L. Oe, A.J.M. Donker, Department of Internal Medicine, Free University, Amsterdam, The Netherlands.* It has been suggested that renal reserve filtration capacity is absent when GFR levels are below 60 ml/min/1.73 m^2. It also has been suggested, however, that early protein restriction in chronic renal failure is beneficial by lowering hyperfiltrationin still functioning nephrons, even when GFR levels are below 60 ml/min/1.73 m^2. We, therefore, investigated the effect of four weeks of low protein diet (LP) and, subsequently, of four weeks of high protein diet (HP) on kidney function in 18 patients with moderate to severe renal failure (GFR =

13-73 ml/min/1.73 M^2), and compared these results with those in five control patients (GFR = 12-73 ml/min/1.73 M^2) who did not change their diet as indicated by their blood and urine urea values. GFR and ERPF were measured simultaneously with ^{125}I-iothalamate and ^{131}I-hippurate, respectively.

	GFR (ml/min/1.73M²)		ERPF (ml/min/1.73M²)	
	LP	HP	LP	HP
$N = 18$	42.2 ± 20.6	46.9[b] ± 22.3	181 ± 77	209[a] ± 94
$N = 5$	37.0 ± 25.0	35.4 ± 24.4	154 ± 103	146 ± 97
	blood urea (mmol/liter)		urea excretion (mmol/24 hr)	
	LP	HP	LP	HP
$N = 18$	8.8 ± 4.3	11.9[b] ± 5.9	195 ± 60	343[b] ± 60
$N = 5$	11.5 ± 4.5	13.2 ± 4.0	275 ± 33	309 ± 55

mean ± SD; [a] $P < 0.005$; [b] $P < 0.001$

The difference in GFR as induced by HP versus LP diet amounted to an average of 10.6% in our test population. No significant change in GFR was observed in the control group. We conclude from these results thatGFR can also vary in moderate to severe renal insufficiency depending on the amount of protein ingested. This indicates a possible reinstatement of the renal reserve filtration capacity by a LP-diet, and might explain the beneficial effect of protein restriction on the progression of chronic renal failure.

Plasma volume (PV) changes during acetate (Ac) and bicarbonate (Bc) dialysis and the influence of left ventricular function. *Leunissen KML, Cheriex E, Janssen J, Teule J, Mooy JMV, van Hooff JP, Department of Internal Medicine, Cardiology and Nuclear Medicine, Academical Hospital, Maastricht, The Netherlands.* In two consecutive weeks, 12 chronic patients were studied during Ac and Bc. Dialysis parameters such as UF were standardized. PV (I^{125}Alb), osmolality (Osm) and colloid oncotic pressure (COP) were measured. Hemodynamic monitoring and echocardiography (M-mode) were done. During Ac, plasma refilling was *considerably* worse compared to Bc (Table) while Osm and COP did not differ. During Ac compared to Bc there was a significant increase in heart rate (HR) and a decrease in mean arterial pressure (MAP) (Table). Cardiac function (fiber shortening velocity-VcF) increased significantly ($P < 0.005$) during Ac and Bc respectively +0.21 and +0.25 circ/sec. Four patients wih a compromised left ventricular function (VcF < 1.0 circ/sec) were studied separately: plasma refilling after ½ hr during Ac was very poor (VFM/VUF_{Ac} 0.9 ± 3.2). It was considerably better during Bc (77.0 ± 9.2) and was almost as good as in patients with a normal left ventricular function. Cardiac function improved during Ac and Bc, but the improvement was more pronounced during Bc, respectively. VcF +0.14 ± 0.09 and +0.25 ± 0.02. In conclusion, PV was considerably better preserved during Bc compared with Ac. This difference is much more pronounced in patients with a compromised left ventricular function. In those patients, Ac is deleterious for PV balance.

Hr	D	VFM/VUF[a]	ΔMAP	ΔHR
½	Ac	8.1 ± 2.6	−13 ± 4.1	+14.1 ± 3.1[c]
	Bc	91.0 ± 8.6[b]	+0.6 ± 2.5[b]	+6.1 ± 1.4
1	Ac	37.1 ± 9.6	−15 ± 4.6	+14.3 ± 2.1[d]
	Bc	79.0 ± 6.2	−4.1 ± 5.4	+ 8.1 ± 1.8
2	Ac	54.8 ± 10.4	−9.2 ± 4.9	+15.4 ± 2.2
	Bc	86.1 ± 5.8[c]	−2.9 ± 4.4	+ 9.7 ± 1.7

[a] extravascular fluid mobilization related to the ultrafiltration volume
[b] $P < 0.001$
[c] $P < 0.01$
[d] $P < 0.05$

Passenger leucocyte dependent prolonged rat renal allograft survival. *P.U.C. Van Breda Vriesman, G.D. Majoor, L. Nagelkerken, Maastricht, The Netherlands.* Well perfused rat kidneys contain at least two sets of passenger leukocytes (PL): radiosensitive, immunocompetent T lymphocytes (10^6 per 1 g) fixed and (5.10^4) capable of migrating out of a renal allograft and relatively fixed, radioresistant dendritic cells. In this study we examined the effect of manipulation of the PL population in the LEWIS (LEW) donor on the rejection of these kidneys in unmodified and LEW-E tolerized Brown Norway (BN) recipients. For this purpose LEW were 900 Rad X-irradiated 48 hr prior to transplantation. X-irradiation of the donor caused a slightly prolonged LEW renal allograft survival (MTS 10 days in unmodified BN recipients, control seven days). When BN recipients were LEW erythrocyte–tolerant, markedly prolonged survival (>70 days) was observed. This prolonged survival could be reduced by prior X-irradiation of the donor kidney (MST 34 ± 4) and was abolished together (MST 11 ± 0.6) when 5.10^6 donor thoracic duct lymphocytes were infused at the time of insertion of the X-irradiated LEW kidney into the tolerized BN recipient. Ia positive dendritic–like cells residing in the thoracic duct lymph caused this effect without breaking tolerance to LEW-E. Passive transfer of 5.10^6 donor thoracic duct cells into tolerized BN recipients of non X-irradiated LEW kidneys did not influence survival. These results show that the markedly prolonged survival of LEW kidneys in tolerized BN recipients requires the presence of radiosensitive donor passenger leukocytes in the graft. Our results suggest that this population is probably a non-mobile population of donor T lymphocytes which exert their effect locally in the graft.

Pseudo Kaposi sarcoma: A distal complication of ciminobrescia arteriovenous fistula. *A.M. Bogaert, R. Vanholder, L. De Keyzer, A. Kint, J. De Roose, S. Ringoir, Department of Nephrology, Dermatology and Surgery, University Hospital, De Pintelaan, 185, 9000 Ghent, Belgium.* Pseudo Kaposi's sarcoma has been associated in most cases with an underlying congenital arteriovenous fistula. Theoretically, this lesion can be expected as well in relation with hemodialysis vascular accesses. Nevertheless, this disease has only once been reported in conjunction with Cimino–Brescia arteriovenous fistulas, and no attention has been paid to the potential complication risks. Recently, we observed three cases within a hemodialysis population of eighty patients. A biopsy was performed in two of the three patients, confirming the preconceived clinical diagnosis. This procedure was followed by local infection and retarded healing of the wound, treated by antibiotics during several weeks. In a third patient pseudo Kaposi's sarcoma was complicated by an infected open wound and septicemia necessitating the administration of i.v. antibiotics. Fistulographic and/or Doppler evaluation revealed venous outflow stenosis in only one case. After reconstruction (one patient) or abandoning the fistula (two patients) correction of the lesions was observed. It is concluded that pseudo Kaposi sarcoma can occur as a distal complication of Cimino–Brescia arterio–venous fistulas. There is a potential risk of serious complications when no corrective measures are taken. The performance of a skin biopsy might be associated with infection and delayed wound healing, so that it should only be obtained in cases of doubt concerning the diagnosis.

Assessment of hyperoxaluria in patients with chronic renal failure. *B.G. Wolthers, S. Meijer, T. Tepper, M. Hayer, Central Laboratory for Clinical Chemistry and Department of Nephrology, University Hospital, Groningen, Groningen, The Netherlands.* An eighteen–year–old boy, dialysed twice a week because of chronic renal failure, was suspected of having hyperoxaluria. In order to prove its presence, plasma oxalate concentrations just before and at the end of dialyses were measured as well as oxalate concentrations in hemodialysate at various moments during dialysis. The obtained values were compared with those derived from a group of 12 other patients, one of them known of having primary hyperoxaluria type I. Oxalate concentrations in plasma and hemodialysate of the known and suspected hyperoxaluric patients were found to be similar and far above those obtained for the remaining non-hyperoxaluric patients. It was concluded that a plasma oxalate concentration above 100 μmol/liter before dialysis and above 25 μmol/liter after dialysis in combination with an oxalate concentration in hemodialysate above 25 μmol/liter at the beginning and above 10 μmol/liter at the end of dialysis, is indicative for hyperoxaluria. From the data obtained for the hemodialysate samples the amount of removed

oxalate during dialysis could be calculated. For patients dialysed twice a week, this amount should be less than 2 mmol in order to exclude hyperoxaluria. Both the suspected as proven hyperoxaluric patient showed values well above this limit. In order to prove that our patient had primary hyperoxaluria type I his plasma glycollate concentration was measured, which was not essentially different from that of the other patients. However, primary hyperoxaluria type I should not be ruled out, as all dialysed patients showed plasma glycollate levels far below those of oxalate, whereas in persons with normal renal function these concentrations were approximately equal. Our results suggest, therefore, that in dialyzed patients a metabolic shift occurs, resulting in more conversion of glyoxalate to oxalate compared with normals making it difficult to prove whether such a patient suffers of primary hyperoxaluria type 1.

Prognostic value of T cell subset ratios for renal graft survival in patients on different immunosuppressive regimens. *F.C. Henny, L.C. Paul, A. van Es, P.J. Oljans, W.M. Baldwin, H.J. Tanke, L.A. van Es, Departments of Nephrology and Cyto- and Histochemistry, University Hospital, Leiden, The Netherlands.* Previously we reported that the pretransplant and pre-rejection OKT4/OKT8 ratio can be used to predict renal allograft survival. Patients on azathioprine (Aza) and low dose steroids (St) with a pretransplant ratio ≤ 1.6 exhibited a six month graft survival of 33% compared with 79% for those with a ratio > 1.6 ($P = 0.02$). Furthermore, 100% of the rejection episodes treated with high doses of prednisone for patients with a prerejection ratio ≤ 1.6 were irreversible in comparison with only 10% for patients with a ration >1.6 ($P < 0.001$). In the present study, we investigated the prognostic value of the OKT4/OKT8 ratio for patients who received rabbit antithymocyte globulin (RATG) as anti-rejection therapy or cyclosporin A (CsA) as basic immunosuppressive therapy. No correlation was found between the pretransplant OKT4/OKT8 ratio and six month graft survival for either treatment group because of an improved graft survival among patients with a pretransplant ratio < 1.6 (78% for patients who received RATG and 85% for CsA-treated patients). For Aza-treated patients, rejection episodes with OKT4/OKT8 ratio ≤ 1.6 that were treated with RATG were reversible in in 78% of the cases, whereas among CsA-treated patients, rejection episodes treated with high doses of prednisone were reversible in 72% of the cases. No significant differences in graft survival or reversibility of rejection episodes in patients with a pretransplant or prerejection OKT4/OKT8 ratio >1.6 were found. Furthermore, in both the CsA and the Aza-treated patients (with or without RATG), the OKT4/OKT8 ratio had significantly decreased three months after transplantation. This decrease was associated with cytomegalovirus infections rather than the type of immunosuppressive therapy.

Treatment of NZB/W female mice with prednisone (PDN), cyclophosphamide (CY) or total lymphoid irradiation (TLI). *M. Waer, B. Van Damme, M. van der Schueren, P. Michielsen, M. Vandeputte, University of Leuven, Belgium.* Nine to 11 month old NZB/W mice with high grade lupus-like glomerulonephritis (proteinuria > 3 g/liter) received daily injections of PDN (5 mg/kg; $N = 18$), weekly pulses of CY (25 mg/kg; $N = 25$) or 17 daily fractions of 2 Gy of TLI ($N = 26$) or no treatment (Control, (Con; $N = 10$). At three months after the start of therapy, none of 10 Con and only three of 18 PDN mice survived, none of the latter showing remission (proteinuria < 1 g/liter). CY therapy was efficient since 57% survival was obtained ($P < 0.01$ vs Con) with remissionin 80% of the surviving mice. TLI was even more effective (survival 87% $P < 0.01$ vs. CY and 94% remission in surviving animals). Higher mortality in CY vs. TLI was due to lymphoma and infections. Both TLI and CY provoked a significant decrease of the activity index and a stabilization of the chronicity index on renal biopsy. Immunofluorescence (IF) remained strongly positive in both groups. Anti-DNA antibodies (ab) were significantly decreased only by CY and not by TLI. In conclusion, both TLI and CY pulse therapy are effective in treating NZB/W glomerulonephritis, but TLI is associated with less side effects. The finding of persistently high anti-DNA ab together wih strongly positive IF despite remission in TLI treated mice suggests that beside anti-DNA antibodies, other mechanisms (cellular?) are also involved in NZB/W lupus-like disease.

Hemodialysis biocompatibility: Dialyzer, dialysate and patient dependent responses. *F. A.A. de Jonge, C. J. Kalkman, M. R. Daha, and M. J. Nubé. Alkmaar Medical Centre and University Hospital Leiden, The Netherlands.* The effect of cuprophane (CU) and cellulose acetate (CA) membranes and of acetate (AC) and bicarbonate (BC) dialysate on neutrophil count, arterial pO_2 and complement activation (CAC) were studied prospectively in three groups of six chronic hemodialysis patients each. In each group, patients were studied during four dialysis sessions ($2 \times$ CU, $2 \times$ CA). Patients in group 1 received AC dialysis only. Patients in group 2 first received 1 hour of isolated ultrafiltration (UF) prior to AC dialysis. Patients in group 3 received BC dialysis only. Within the first 30 minutes, neutropenia occurred in all three groups, being significantly greater for CU than CA. Hypoxemia occurred only during AC dialysis (group 1; group 2, after UF) and did not occur during BC dialysis (group 3) or UF (group 2). CAC, as measured by C3d levels, occurred to a variable degree in all three groups, but no significant difference between CU and CA was found. Analysis of variance identified two patient subgroups: one group ($N = 4$) with rebound leucocytosis after 60 minutes of dialysis on CU with relatively high CAC, and a second group ($N - 3$) without rebound leucocytosis on CU with substantially less CAC. Furthermore, in the first group, neutrophil counts after 60 minutes of dialysis on CA were more depressed than in the second group. We conclude that: *(1)* neutropenia and hypoxemia are independent phenomena, the first membrane, the second dialysate dependent; *(2)* individual (as yet unknown) patient factors influence the neutrophil response and possibly CAC to a larger degree that hitherto assumed.

Renal biopsy findings in 65 children with isolated hematuria. *C.H. Schröder, C.M. Bontemps, K.J. Assmann, J.M. Foidart, J.H. Schuurmans Stekhoven, J.H. Veerkamp, L.A. Monnens, Departments of Pediatrics, Pathology and Biochemistry, St. Radboud Hospital, University of Nijmegen, The Netherlands, and Dept. of Obstetrics, Bavière Hospital, University of Liège, Belgium.* It remains controversial point that isolated hematuria in childhood should be investigated by renal biopsy involving all available techniques. To elucidate this point, a renal biopsy was performed in 65 children with isolated hematuria persisting for at least one year. The renal biopsy was studied by light microscopy, immunofluorescence and electronmicroscopy. In all these children glomerular filtration was normal. Proteinuria, hypercalciuria, and hypertension were absent. In 14 children the diagnosis of IgA nephropathy was made, in eight children the diagnosis of Alport syndrome and in five children the diagnosis of post-infectious glomerulonephritis. Thirty-three children were classified as having benign hematuria. Over half of these cases appeared familial. By electronmicroscopy all Alport patients showed typical findings: diffuse or focal thickening and splitting of the glomerular basement membrane (GBM), irregular alternation of thick, thin and normal GBM. In benign hematuria GBM was thin (<250 nm) over more than 50% of its measured length in half of the studied children. Smaller percentages were present in the others. Biopsies of children suffering from Alport syndrome (6) and benign hematuria (6) were investigated by immunofluorescence using specific anti-GBM component antisera (collagen IV, laminin, fibronectin, proteoglycan and Goodpasture) and compared with results obtained in biopsies from children with nephrotic syndrome and minimal lesions. Only the activity of anticollagen IV was slightly diminished in benign hematuria and Alport syndrome. The Goodpasture antiserum gave variable results in Alport syndrome. A positive immunofluorescence was always present in benign hematuria. Studies by immunofluorescence and electronmicroscopy are required to differentiate isolated hematuria in childhood. They are important for the prognosis of these children and for genetic counseling. Abnormal histology was present in 62 out of 65 children in contrast with the results of the unique similar study of Trachtman et al., who were unable to detect abnormalities in 33 out of 76 children.

The beneficial effect of indomethacin on final renal outcome in nephrotic patients. *R Vriesendorp, P E de Jong, W J Sluiter, D de Zeeuw, A J M Donker, G K van der Hem, Division of nephrology, University Hospital, Groningen, the Netherlands.* To study the influence of indomethacin as antiproteinuric agent on renal function decline and final renal outcome in nephrotic patients, a retrospective study was

undertaken. One hundred and fourteen patients were identified with a proteinuria of more than 3 g per day and with a diagnosis membranous glomerulopathy, focal glomerulosclerosis, or membranoproliferative glomerulonephritis out of the renal biopsy records from 1968 to 1984. Those diagnosis groups were selected because they were not routinely treated with corticosteroids. Sixteen patients were excluded because of follow–up less than six months. Fifty–eight patients had been treated with indomethacin for at least half a year, while the other forty patients acted as their untreated controls. As assessed by log rank analysis, renal survival was significantly superior in the indomethacin–treated patients over the untreated patients. At ten years follow-up, 31 percent of the treated and 66 percent of the untreated patients needed dialysis ($P < 0.05$). Renal function decline was assessed by creatinine doubling time. Indomethacin treatment, serumcreatinine, mean arterial pressure, proteinuria, serum albumin, age, sex, and diagnosis were evaluated for their prognostic significance by log rank analysis of the creatinine doubling life tables. In this univariate analysis, proteinuria and diagnosis influenced the rate of renal function decline significantly. Heavy proteinuria and membranoproliferative glomerulonephritis were associated with a rapid doubling of serum creatinine. In the subset of patients with a serum creatinine less than 110 μmol per liter, indomethacin delayed creatinine doubling significantly. In this retrospective study the use of indomethacin as antiproteinuric agent appeared to have a beneficial effect on long–term renal survival in nephrotic patients. This hold especially true in patients with a serum creatinine less than 110 μmol per liter at the start of treatment.

Dysplasia and hypoplasia in refluxing kidneys of patients with renal failure. *B. van Damme, R. Oyen, Y. van Renterghem Leuven, Belgium.* Reflux nephropathy is an important cause of renal failure. In refluxing kidneys different scars have been described: pyelonephritic scars, reflux scars, and dysplasia or hypoplasia. Dysplasia is defined by the presence of 'primitive' tubules surrounded by concentric loose connective tissue. Hypoplasia is defined by the absence of normally formed nephrons or the evident scarcity of nephrons in a segment of the kidney. In 21 patients with radiologically proven reflux of at least grade II, one or both kidneys removed as a pretransplant procedure were retrospectively analysed for the presence of these scars. Hypoplasia and/or dysplasia was present in 17 patients, combined with reflux scars in 13, pyelonephritic scars in one, and reflux and pyelonephritic scars in two. Only four patients did not have features of dysplasia or hypoplasia. These data suggest that congenital malformation of the kidney may be a major factor in the eventual destruction of renal structure and function. This might also explain why reparative surgery on refluxing kidneys does not alter the outcome of the reflux nephropathy and why new scars are only seldom found during follow–up of reflux nephropathy.

Recurrent peritonitis in CAPD: Survival and growth of bacteria within human mononuclear phagocytes as a possible mechanism. *H. van Bronswijk, H.J. Bos, H.A. Verbrugh, P.L. Oe, J. Verhoef, A.J.M. Donker, Free University Hospital, Amsterdam, and State University of Utrecht, The Netherlands.* Patients treated by CAPD may suffer from frequent bouts of peritonitis, frequently due to Staphylococcus epidermidis (SE). Recurrence or persistence of SE infection may reflect intraleukocytic sequestration of bacteria that remain viable inspite of antimicrobial therapy. We studied survival and growth of SE after phagocytosis by human polymorphonuclear leukocytes (PMN), monocytes (MN) and peritoneal macrophages (PMO). PMN, MN and PMO ingested equal numbers of opsonized SE: from the 5×10^6 SE colony forming units (CFU) inoculum, $1.0\text{-}3.5 \times 10^5$ SE cfu remained viable after one hour incubation indicating comparable initial killing rates of SE in PMN, MN and PMO. Electronmicroscopy (EM) showed intact as well as desintegrating SE within phagolysosomes. Subsequently, phagocytes were washed to remove free SE and incubated for 18 hours in the presence of minimal inhibitory concentrations of cefamandol (CF), clindamycin (CL), or rifampicin (RF). In the presence of CF PMN-associated SE cfu decreased 7 ± 2 (mean ± SEM) fold; in contrast, MN and PMO-associated SE cfu increased 17 ± 6 fold and 26 ± 9 fold, respectively. In the presence of CL or RF, however, SE cfu decreased significantly in all three types of phagocytes. EM at 18 hours revealed increased numbers of SE in MN, but not in PMN incubated with CF. We conclude that SE survives and grows in human MN and PMO, but not in PMN. Secondly, the ability to suppress intracellular growth of SE seems to be an important requirement for optimal antibiotic treatment of SE infections.

Important role for mannitol in the prevention of acute renal insufficiency after cadaveric transplantation. *P.L.J. van Valenberg, A.J. Hoitsma, R.G.W.L. Tiggeler, J.H.M. Berden, H.J.J. van Lier, R.A.P. Koene, Division of Nephrology, Sint Radboudziekenhuis, Nijmegen.* With its incidence at about 40%, acute renal insufficiency (ARI) is a major problem after cadaveric renal transplantation. We have previously shown that with moderate hydration (2.5 liters) of the recipient together with rapid infusion of 250 ml Mannitol 20% (MA) just before clamp removal, the incidence of ARI decreased to below 10%. Administration of MA without hydration was not effective. In a prospective randomized trial we have now investigated whether hydration without MA is sufficient to prevent ARI. We defined ARI as a urine volume of less than 400 ml per 24 hours. All recipients received moderate hydration. Patients were randomly treated with either cyclosporin (CS) or azathioprine (AZ). In both treatment groups, recipients were randomized to treatment with either MA or placebo (250 ml glucose 5%, GL). The statistical method used to allocate patients made balance in advance for sex, age of the donor and the recipient, DR mismatches, number of previous transplantations, DRW6 antigen, anti-lymphocyte antibodies, and total cold ischemia time. In the four treatment groups, factors concerning the donors (diuresis and blood pressures before nephrectomy, and serum creatinine) and the recipients (total amount of fluid infused during the operation, per operative blood pressures, method of kidney replacement therapy before transplantation, original kidney disease, and serum urea) were the same. In the CS-group, the percentage of ARI was significantly lower in MA-treated ($N = 32$) than in GL-treated patients ($N = 32$) (9 vs. 34%, $P < 0.05$). In the AZ-group the percentage of ARI was also lower in MA-treated ($N = 33$) than in GL-treated patients ($N = 34$) (18 vs. 44%, $P < 0.05$). Overall evaluation of ARI in both groups showed a significant difference in favour of MA-treatment ($P = 0.001$). Thus, moderate hydration and administration of 250 ml mannitol 20% just before arterial clamp release are both indispensable for optimal prevention of ARI after cadaveric transplantation.

The influence of cyclosporine on renal allograft survival and function. *F.C. Henny, A.A.M. Kootte, J.H. van Bockel, W.M. Baldwin, J. Hermans, B. Bos, L.A. van Es, L.C. Paul, Departments of Nephrology, Surgery, and Medical Statistics, University Hospital, Leiden, The Netherlands.* To study the effectiveness and nephrotoxic side–effects of Cyclosporin A (CsA) in renal transplant recipients, a prospective randomized trial was designed in which CsA was compared with Azathioprine (Aza). Fourty patients had entered in each treatment group; in the CsA group, 18 were randomly selected for conversion to Aza after three months. The one–year graft survival in CsA-treated patients was 87% compared with 66% in the Aza-treated patients ($P = 0.033$). The incidence of one or more rejection treatments was 75% in the Aza-treated group compared with 45% in the CsA group ($P = 0.01$). The incidence of primary non-functioning kidneys, cytomegalovirus infections, hypertension, and degree of proteinuria did not differ in the two treatment groups. At three months the mean endogenous creatinine clearance was 42 ± 2 ml/min (mean ± SEM) in the CsA-treated group compared with 56 ± 4 ml/min in the Aza group ($P < 0.001$), whereas at six months the mean creatinine clearances for both the converted and non-converted CsA-treated patients did not differ from that found for the Aza-treated group. At one year, the mean creatinine clearances found for CsA-treated patients who were converted to Aza and for those who remained on CsA-therapy were higher than in the Aza-treated patients (62 ± 7 and 55 ± 3 ml/min, respectively, vs. 50 ± 6 ml/min; $P < 0.05$). Furthermore, the increment in creatinine clearances observed after conversion from CsA to Aza showed a linear relationship ($r = 0.9061$) with the CsA trough levels before discontinuation of the drug. This indicates that CsA treatment induces a dose–dependent, nephrotoxic side effect which is probably reversible.